The ICH M13A guideline on bioequivalence (BE) for immediate-release (IR) solid oral dosage forms.
Recommendations for innovators and generic drug products

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ABSTRACT

On December 2022, the ICH Assembly endorsed the ICH M13A guideline, the first of the three in the series to describe the scientific and technical aspects of study design and data analysis to support BE assessment during both development and post-approval phases for orally administered IR solid oral dosage forms. The ICH M13B about biowaiver considerations for additional strengths not investigated in BE studies and ICH M13C about complex BE study design are currently in preparation. A randomised, single-dose, two-period, two-sequence crossover study design is recommended by the ICH M13A guideline when comparing two formulations:

- The number of subjects to be included in the BE study should be based on an appropriate sample size calculation to achieve a pre-specified power and type-1 error.
- The highest to be-marketed strength should be used.
- The administration in fasting or fed conditions or both, as well as the meal type and the water intake should be based on the properties of the Comparator Product and the Test Product (high or non-high risk). The rationale can be supported by modelling, e.g., appropriately validated/qualified physiologically based pharmacokinetic (PBPK) modelling or semi-mechanistic absorption models.
- The sampling times should ensure reliable estimates of maximum concentration (C_{max}), terminal rate constant (k_{el}) and extent of exposure (i.e., $AUC_{(0\text{-}t)}$ should cover at least 80% of $AUC_{(0\text{-}inf)}$).
- Treatment periods should be separated by a sufficiently long washout period, e.g., at least 5 elimination half-lives ($t_{1/2}$).
- The Sequence, Subject within Sequence, Period, and Formulation effects should be tested by ANOVA.
- The assessment of BE should be based on the 90% confidence interval (CI) of the geometric mean ratio (Test/Comparator) for the primary PK parameters under consideration. The 90% CI should lie within the range of 80.00 - 125.00%. For single dose studies, primary parameters for BE analysis, estimated by non-compartmental methods, should include $AUC_{(0\text{-}t)}$, C_{max}, and, where applicable, partial AUC (pAUC) or $AUC_{(0\text{-}72)}$. Additional parameters should include $AUC_{(0\text{-}inf)}$, peak time (T_{max}), k_{el}, and $t_{1/2}$. The recent draft FDA guidance "Statistical Approaches to Establishing Bioequivalence", issued on December 2022, exhaustively complements these statistical rules for BE comparisons.

A parallel design may be employed for drugs with long elimination $t_{1/2}$, when a crossover design is impractical due to the need for a prolonged washout period.

A multiple-dose study with an appropriate number of dosage administrations to reach steady-state (SS) may be conducted in patients, if a single-dose study cannot be conducted in either healthy subjects for safety and/or tolerability reasons or in patients for ethical reasons. For SS studies, the primary parameters for BE analysis should be C_{maxSS} and $AUC_{(0\text{-}tauSS)}$. Additional parameters should include C_{tauSS}, C_{minSS}, C_{avSS}, degree of fluctuation, and T_{max}. Finally, specific topics of the ICH M13A guideline deal with endogenous compounds, orally disintegrating tablets, chewable tablets, oral suspensions, and fixed dose combinations.

The draft ICH M13A has been released for comments until May 26 , 2023 in EU.

INTRODUCTION

Current regional or multi-regional guidelines have different views and criteria regarding design of BE studies and data analysis. This lack of harmonisation can result in product developers having to follow different approaches in different regions and conducting additional BE studies, hampering a streamlined global drug development. These issues create unnecessary burden on product developers and result in potentially limiting or delaying access to affordable drugs to patients.

Objective of the ICH M13 guideline is to harmonize the criteria of BE study design and data analysis among international competent authorities by establishing common regulatory requirements in multiple jurisdictions on conducting BE studies during both development and post approval phases for orally administered IR solid oral dosage forms designed to deliver drugs to the systemic circulation, such as tablets, capsules, and granules/powders for oral suspension. The pharmacokinetic (PK) principles of this guideline will also be generally applicable to non-orally administered drug products with immediate action, e.g., certain rectal, inhalation, and nasal drug products. The ICH M13 guideline includes the following three tiers:

Tier 1 → M13A: Focus on scientific and technical aspects of study design and data analysis to support BE assessment for orally administered IR solid oral dosage forms.

Tier 2 → M13B: Focus on BE for additional strengths of a product line including biowaiver considerations.

Tier 3 → M13C: Focus on BE study design, analysis, and assessment for highly variable drugs, drugs with narrow therapeutic index (NTI) and complex BE study design and analysis considerations.

ICH M13 Workplan

ICH	Start	Step 1 Consensus building	Step2 Draft guideline	Step3 Public and Regulatory consultation and discussion	Step4 Adoption of an ICH harmonized guideline
M13 A	Jul 2020	Dec 9, 2022	Dec 20, 2022	Jul 2023	May 2024
M13 B	Nov 2023	Nov 2023	Jan 2023	-	-
M13 C	Jul 2024	-	-	-	-

Currently, the ICH M13A has been released by the regulatory authorities of the ICH regions for internal and external consultation, according to national or regional procedures. The main contents are highlighted below.

ICH M13A: General principles in establishing bioequivalence

Study population: BE studies should be normally performed in healthy subjects unless the drug carries safety concerns that make this approach unethical. This is regarded as adequate in most instances to detect formulation differences and to allow extrapolation of the results to populations for which the product is intended. Subjects should be at least 18 years of age and preferably have a Body Mass Index between 18.5 and 30.0 kg/m^2. If a drug product is intended for use in both sexes, it is recommended the study include male and female subjects. Female subjects should not be pregnant or lactating during the BE study and the follow-up. Subjects should preferably be non-nicotine users and without a history of alcohol or drug abuse. Phenotyping and/or genotyping of subjects may be considered for safety or PK reasons.

Study design: A randomised, single-dose, two-period, two-sequence crossover study design is recommended when comparing two formulations. Treatment periods should be separated by a sufficiently long washout period, e.g., at least 5 elimination $t_{1/2}$. In general, the highest to be-marketed strength should be used in a BE study. If this cannot be administered to healthy subjects for safety and/or tolerability reasons, a single-dose study conducted in healthy subjects using a lower strength may be possible or, alternatively, a single-dose study in patients using the highest proposed strength could be considered. A multiple-dose study may be conducted in patients if a single-dose study cannot be conducted in either healthy subjects for safety and/or tolerability reasons or in patients for ethical reasons. The study protocol should include an appropriate number of dosage administrations to reach steady-state. For drugs with long $t_{1/2}$, a parallel design may be employed when a crossover design is impractical due to the need for a prolonged washout period.

Sample Size: the number of subjects to be included in the BE study should be based on an appropriate sample size calculation to achieve a pre-specified power and pre-specified type 1 error. A sufficient number of subjects should be enrolled in the BE study to account for possible dropouts and/or withdrawals. The number of evaluable subjects in a pivotal BE study should not be less than 12 for a crossover design or 12 per treatment group for a parallel design.

Test Product: it should be representative of the product to be marketed. For pivotal BE studies, it should originate from a batch of at least 1/10 of production scale or 100,000 units, whichever is greater. The assayed content of the batch used as Test Product should not differ by more than 5% from that of the batch used as Comparator Product.

Comparator Product: drug product accepted by regulatory authorities that can be used to compare to the Test Product. The selection of the batch should be based on assay content. It is advisable to investigate more than one batch when selecting the batch for use in the BE study. Study designs containing multiple Comparator Products or Test Products are included in M13A to take some initial steps to reduce the associated burden without prejudice to regional legal requirements.

Fasting and/or Fed Conditions: for the majority of drug products, BE may be demonstrated in a single study under fasting conditions, which typically provide greater discrimination between the PK profiles of two products. The design of a BE study with regard to the use of fasting and/or fed conditions and meal type (e.g., fat and calorie content) depends on the dosing instructions of the Comparator Product, the properties of drug substance and the properties of the Comparator and Test Products ("high-risk" or "non-high risk"). The rationale can be supported by validated/qualified physiologically based pharmacokinetic (PBPK) modelling or semi-mechanistic absorption models.

High-Risk Products (risk of BE Failure): products where the complexity of the formulation design or manufacturing process leads to an increased likelihood that in vivo performance will be impacted differently by varying gastrointestinal conditions between the fasting and fed states. Performance differences related to differences in formulation and/or manufacturing process may not be detected with a single BE study, i.e., results from a fasting BE study may not be extrapolated to predict fed BE study outcome or vice versa, thus both fasting and fed BE studies should be conducted.

Meals and water: For studies conducted under fasting conditions, subjects should be fasted for at least 10 h before administration, be allowed water as desired, except for 1 h before and 1 h after administration. The dose should be administered with a standardised volume of water, in the range of 150 to 250 mL. No food should be allowed for at least 4 hours post-dose on each day of drug administration and meals taken should be standardised with respect to composition and timing. In the case of studies under fed conditions, a pre-dose meal should be provided starting 30 min before administration. The meal should be consumed within 30 min.

Dose or Strength: In case of an application with multiple strengths, the strength to be used depends on the dose proportionality in PK and solubility of the analyte. Generally, the highest to-be marketed strength can be administered as a single unit. Selection of a lower strength may also be accepted if the highest strength cannot be administered to healthy subjects for safety and/or tolerability reasons and dose proportional PK. In case of more than dose proportional increase in exposure, the highest strength should be used. In case of less than dose proportional increase in exposure, the lowest strength should be used if non-proportionality is due to saturation of absorption, the lowest and the highest strength if due to solubility or unknown reason.

Moieties to be measured: demonstration of BE should be based on the analysis of the parent drug because its concentration-time profile is usually considered more sensitive to detect a difference between formulations than metabolite data. This also applies to prodrugs. If prodrugs are rapidly eliminated it is acceptable to demonstrate BE based on a primary metabolite without measurement of the parent compound. In rare cases, demonstration of BE based on the parent drug alone may not be sufficient and the primary active metabolite should also be considered.

Enantiomers vs. racemates: use of an achiral bioanalytical assay to measure the racemate is generally acceptable. A stereoselective assay measuring individual enantiomers should be employed in some cases. It is sufficient to demonstrate BE for only the active enantiomer in cases where one enantiomer is inactive (or makes a low contribution) with respect to both safety and efficacy.

Collection and analysis of samples: a proper blood sampling schedule should be applied to obtain a reliable estimation of the absorption phase, the T_{max} and the extent of exposure, which is achieved when $AUC_{(0\text{-}t)}$ covers at least 80% of $AUC_{(0\text{-}inf)}$. This period is usually at least three times the terminal $t_{1/2}$ of the drug, unless a suitable truncated AUC, e.g., $AUC_{(0\text{-}72h)}$, is used. Three or more data points in the terminal phase of the concentration time curve should be used to estimate k_{el}. Truncating AUC is allowed for drugs that exhibit long elimination $t_{1/2}$. For such products, $AUC_{(0\text{-}72h)}$ may be used in place of $AUC_{(0\text{-}t)}$. When the early onset of action is clinically relevant, pAUC, may be estimated. This pAUC is typically evaluated from the time of drug administration until a pre-determined time point that is related to a clinically relevant pharmacodynamic measure. Drug concentrations in study samples should be measured in accordance with ICH M10 "Bioanalytical Method Validation and Study Sample Analysis".

Data analysis: Single-dose PK parameters to be estimated are the primary parameters $AUC_{(0\text{-}t)}$ or $AUC_{(0\text{-}72h)}$, C_{max}, and pAUC, where applicable. Additional parameters are $AUC_{(0\text{-}inf)}$, $AUC_{(0\text{-}t)}/AUC_{(0\text{-}inf)}$, T_{max}, k_{el}, $t_{1/2}$. $AUC_{(0\text{-}t)}$ should cover at least 80% of $AUC_{(0\text{-}inf)}$, except in case AUC is measured over 72 hours. Standard statistical approaches should be employed. Non-compartmental methods used to derive the PK parameters from the raw data should be reported, e.g., linear trapezoidal method for AUC and the number of data points of the terminal log-linear phase used to estimate k_{el}. Any concentration reported as below the lower limit of quantification (LLOQ) should be treated as zero in PK parameter calculations. Values below the LLOQ are to be omitted from the calculation of k_{el} and $t_{1/2}$. For multiple-dose studies, applicants should document appropriate dosage administration and sampling to demonstrate the attainment of steady-state. The PK parameters to be tabulated are primary parameters C_{maxSS} and $AUC_{(0\text{-}tauSS)}$, and additional parameters for analysis: C_{tauSS}, C_{minSS}, C_{avSS}, degree of fluctuation, swing, and T_{max}.

Statistical and Bioequivalence Analyses: Conventional two-treatment, two-period, two-sequence randomised crossover design studies should be analysed using an appropriate parametric method, e.g., ANOVA, by testing Sequence, Subject within Sequence, Period, and Formulation effects. The assessment of BE is based on 90% confidence intervals for the geometric mean ratios (Test/Comparator) for the primary PK parameters under consideration, which should lie within a range of 80.00 - 125.00%.

Multiple Comparator Products: It may be necessary to demonstrate BE between a Test Product and multiple Comparator Products to meet requirements from multiple jurisdictions. In such case, including Comparator Products from different regions in one trial is acceptable to streamline the BE demonstration by conducting one single higher-order crossover BE study with multiple Comparator Products.

Multiple Test Products: It may be necessary to demonstrate BE between multiple Test Products and the Comparator Product. To streamline the demonstration of BE, it is permitted to conduct one single crossover BE study with multiple Test Products.

Specific topics: sections of the M13A guideline are dedicated to endogenous compounds, other IR dosage forms (i.e., orally disintegrating tablets, ODT, chewable tablets, oral suspensions, fixed-dose combinations), and to the pH-dependency, this latter addressing issues related to drug substances with pH-dependent solubility. The absorption of these drug substances may in fact be influenced by the gastric pH and be altered due to the use of, for instance, pH stabilising excipients or a specific salt-form in the formulation. Modelling may be used to assess the risk of bioinequivalence.

CONCLUSIONS

The ICH M13 guideline is built on steps the agencies have been taking to reduce duplicative BE studies and R&D costs. It also takes action as an important leverage to avoid drug shortages and give available alternatives to the care of patients. ICH M13A is the first effort on this way. The whole process of harmonization will continue with ICH M13B and ICH M13C.

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